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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/196,673	11/20/98	MCCAFFERTY J	28111/32106B

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EXAMINER	
PONNALURI, P	
ART UNIT	**PAPER NUMBER**
1627	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/196,673	Applicant(s) McCafferty et al
	Examiner P. Ponnaluri	Group Art Unit 1627

☒ Responsive to communication(s) filed on *Oct 10, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *45-145* is/are pending in the application.

Of the above, claim(s) *66-77 and 110-144* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *45-65, 78-109, and 145* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *13*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The amendment filed on 10/10/00 has been fully considered and entered into the application.

2. New claim 145 has been added and claim 44 has been canaled by the amendment filed on 10/10/00,

3. claims 45-145 are currently pending in this application.

4. Claims 66-77, 110-144 withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected . Election was made **without** traverse in Paper No. 6.

5. Claims 45-65, 78-109 and 145 are currently being examined in this application.

6. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copies have been filed in parent Application No. 07/971,857.

7. The drawings filed on 11/20/98 were objected by the draftsperson (see PTO 948). Applicant is invited to notice that boxes 5-6 and 12 in PTO 948 were checked by the draftsman. Applicant is encouraged to amend the specification so that the description of renumbered figure corresponds to the renumbered figures.

8. Applicants are requested to delete blank space in specification page 111.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 45-65, 78-109, 145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Briefly the claims are drawn to a method of producing a specific binding pair member, the specific binding pair member comprises an enzyme or fragment thereof which is 100-200 amino acids, and the method comprises by expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides provided by mutating nucleic acid encoding the specific binding pair member, and the polypeptides are displayed on the surface of a filamentous phage particles , and selecting the phage particles that display the polypeptide (which is enzyme or fragment thereof) which bind to the desired ligand, and obtaining the specific binding pair member from the nucleic acid of the selected phage.

The specification discloses phage display library of alkaline phosphatase (a dimer) (in examples 11 and 12) and a nuclease (example 36), which meets the written description and the specification disclosure clearly do not provide an adequate representation regarding the open ended claimed method of producing all known enzymes. However, the instant claims are directed to phage display library of all the known enzyme. None of which meet the written description provision of 35 U.S.C 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of library of alkaline phosphatase and a nuclease, the skilled artisan cannot envision the method of making the libraries of other enzymes which would be displayed on the surface of a filamentous phage. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* ,

107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only method for producing specific enzymes, but not the full breadth of the claim meet the written description provision of 35 U.S.C 112, first paragraph.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 45-65 and 78-109 and 145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 145, 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to produce a member of specific binding pair. The independent claim recites a method of obtaining a member of specific binding pair, and the

method comprises: expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides. However, the claimed method is incomplete, because the claim does not say how the specific binding pair is produced from the phage particles. The claim does not include method steps in which the recombinant host cells are screened or selected for phage particles displaying the specific binding pair, and obtaining nucleic acid encoding the specific binding pair from the selected phage particles . The claims lack steps in which the host cells expressing the specific binding pair are selected by affinity selection in presence of a ligand.

Claim 48 is indefinite by reciting ' a mixed population of displayed polypeptide specific binding pair members', it is not clear what does applicant mean by mixed population of displayed polypeptide. Does applicant mean mixed population of phage displaying polypeptides or mixed population of polypeptides displayed on the phage? It is confusing, because claim 145 recites that at the surface of the phage the polypeptide is displayed. Applicants are requested to clarify.

Claims 55 and 57 are vague by reciting in step (ii), producing from nucleic acid obtained in step (I) nucleic acid which encodes a specific binding pair member. It is not clear what does applicant mean by producing nucleic acid from the nucleic acid obtained in step I), because the nucleic acid obtained in step I), is the nucleic acid which encodes the member of specific binding pair. Does applicant mean that the affinity purification or selection of phage particles that display the specific binding pair member is repeated, it is not clear.

Claims 60-65 are vague and indefinite by reciting in step (ii) ' nucleic acid which encodes a derivative specific binding pair member..', it is not clear what does applicant mean by derivative specific binding pair member. It is not clear whether the derivative specific binding pair member has similar properties as the specific binding pair member and does it bind specifically to the ligand of interest. The deletions, substitution or insertions of amino acids might change the binding characteristics of the specific binding pair member. It is also not clear what does applicant mean by the linkage of another molecule, what is the another molecule. Is it another peptide which might alter the peptide which is encoded by the nucleic acid obtained in step (I) or a marker. Applicants are requested to clarify what is the derivative of specific binding pair member.

Claims 78-85 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to produce a specific binding pair member from the particle displaying the specific binding pair member. The instant claims are drawn to a method of obtaining a member of a specific binding pair, by contacting a library of filamentous bacteriophage particles with a desired ligand and separating particles displaying a specific binding pair members which bind to said desired ligand. However, the claimed method fails to teach how to get the specific binding pair member displayed by the particle . Applicants are suggested to include all the method steps.

Claims 94-101 are vague by reciting in step (ii), producing from nucleic acid obtained in step (I) nucleic acid which encodes a specific binding pair member. It is not clear what does

applicant mean by producing nucleic acid from the nucleic acid obtained in step I), because the nucleic acid obtained in step I), is the nucleic acid which encodes the member of specific binding pair. Does applicant mean that the affinity purification or selection of phage particles that display the specific binding pair member is repeated, it is not clear. Applicants are requested to clarify.

Claims 102-109 are vague and indefinite by reciting ' nucleic acid which encodes a derivative specific binding pair member..', it is not clear what does applicant mean by derivative specific binding pair member. It is not clear whether the derivative specific binding pair member has similar properties as the specific binding pair member and does it bind specifically to the ligand of interest. The deletions, substitution or insertions of amino acids might change the binding characteristics of the specific binding pair member. It is also not clear what does applicant mean by the linkage of another molecule, what is the another molecule. Is it another peptide which might alter the peptide which is encoded by the nucleic acid obtained in step (I) or a marker. Applicants are requested to clarify what is the derivative of specific binding pair member.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 46, 48-49, 78-81, 86-89 and 94-97, 145 (newly added) are rejected under 35

U.S.C. 102(e) as being anticipated by US Patent 5,427,908 (Dower et al)(102 (e) reference, because of filing date May 1, 1990).

The claims are drawn to a method of producing a specific binding pair member, the specific binding pair member comprises an enzyme or fragment thereof which is 100-200 amino acids, and the method comprises by expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides provided by mutating nucleic acid encoding the specific binding pair member, and the polypeptides are displayed on the surface of a filamentous phage particles , and selecting the phage particles that display the polypeptide (which is enzyme or fragment thereof) which bind to the desired ligand, and obtaining the specific binding pair member from the nucleic acid of the selected phage.

Dower et al teach a method for screening a DNA library for a nucleotide sequence which encodes a protein of interest, and the protein of interest of the invention is an antibody or fragment thereof (Fab) or proteins such as hormones, enzymes, interferons or zymogen (see column 3, lines 19-25) which has a desired binding specificity. Dower et al teach when the desired protein is an immunoglobulin, a library expressing antibody light chain binding regions is combined with a library expressing antibody heavy chain regions, thereby constructing combinatorial Fab expression libraries (see column 4, lines 65-68, column 5, line 1). The reference teaches that the method comprises the following steps: expressing in a recombinant host organism a first polypeptide chain of a specific binding pair fused to a component of a secreted replicable genetic display package that displays the polypeptide at the surface of the package and expressing

in a recombinant organism a second polypeptide chain of said multimer and allowing the polypeptide chains to come together to form a multimer(see column 2, lines 51-59). Dower et al teach that the preferred vectors are filamentous phage fd, f1, and M13 (see column 2, lines 47-48). The reference teaches expression of nucleic acid of each polypeptide chain that is capable of being packaged as replicable genetic display package (see columns 1-2). The reference teaches a method to obtain nucleic acid encoding at least one of said first and second polypeptide chains from a library of nucleic acids encoding said chain (see column 12, lines 49-50). Dower et al teach fusion with pIII coat protein (capsid protein) thus the fusion with the capsid protein is displayed on the phage coat protein while the non-fused protein is expressed in wild type form. The reference teaches that a DNA library is constructed by cloning cDNA (vH region) from the donor cells into a coat protein gene (gene III) cloning site, and the cloning sequences (vH domains) are ultimately expressed as polypeptides up to 120 amino acids (refers to the specific binding pair member comprises an enzyme or fragment thereof and is at least 100 amino acids of the instant claims). The reference teaches although a large peptide fragment near the N-terminus of the coat protein may cause a decrease in phage infectivity and/or yield compared to phage with smaller, but the larger fragments may still be effectively enriched by subsequent rounds of panning (see column 8). The reference teaches that the host cells are then infected with the phage and cultivated under conditions allowing for expression and assembly of phage particles, and the appropriate host cells for bacteriophage are various strains of E.coli (see column 6, lines 23-25). The reference method teaches to isolate phage which contain cloned library sequences which

encode a desired protein and thus to ultimately isolate the nucleic acid sequences, phage harvested from the bacteria are affinity purified (see column 6, lines 54-58). Dower et al teach that the phage identified having an antibody recognized by the target are selected and DNA prepared and sequenced by standard methods to determine DNA and amino acid sequence of the particular antibody, and the DNA may be recloned in a suitable eukaryotic or prokaryotic expression vector and transfected into an appropriate host for production of large amounts of protein (see column 12).

Dower et al teach that the disclosed method of screening a DNA library for nucleotide sequence which encodes a protein of interest is typically an antibody or fragment thereof, but may also be any protein which may be cloned from a nucleotide library, and such proteins include, for example, hormones, interferons, interleukins and enzymes (see column 3, lines 18-24, in particular). Dower et al teach antibodies with catalytic activities (refers to enzymatic activity of the instant claims) may be enriched in groups of antibodies with high affinity for reactants but low affinity for products. A double screen to enrich for antibodies with these characteristics is useful in finding antibodies to catalyze reactions, and catalytic antibodies (refer to enzyme of the instant claims) capable of certain cleavage reactions may be selected using the disclosed method. For example a catalytic antibodies (refer to enzymes of the instant claims) capable of cleavage a specific amino acid from the end of a peptide (refers to desired ligand of instant claims) may be selected by immobilizing the peptide and panning the antibody library under conditions to promote binding but not cleavage and followed by wash, this allows antibodies that recognized the end

group to bind and become immobilized, and to separate the antibodies capable of cleavage, the conditions are shifted in favor of cleavage, which would release the antibody-phage capable of cleavage from the immobilized peptide (see column 11, lines 29-51, in particular).

Dower et al teach that the method can be applied in therapeutic, diagnostic applications, and in preparation of catalytic antibodies. Dower et al teach that the disclosed method facilitate the screening process, thereby enabling DNA sequences which encode protein of interest, and particularly antibody molecules to be recloned and expressed, and these procedures may be used to obtain an antibody to a preselected target molecule, thus, the difficulties and labor intensive process of generating monoclonal antibodies may be avoided. The reference clearly anticipates the claimed invention.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 45-65 and 78-109 and 145 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,427,908 (Dower et al).

Dower et al teach a method for screening a DNA library for a nucleotide sequence which encodes a protein of interest, and the protein of interest of the invention is an antibody or fragment thereof (Fab) or proteins such as hormones, enzymes, interferons or zymogen (see column 3, lines 19-25) which has a desired binding specificity. Dower et al teach when the desired protein is an immunoglobulin, a library expressing antibody light chain binding regions is combined with a library expressing antibody heavy chain regions, thereby constructing combinatorial Fab expression libraries (see column 4, lines 65-68, column 5, line 1). The reference teaches that the method comprises the following steps: expressing in a recombinant host organism a first polypeptide chain of a specific binding pair fused to a component of a secreted replicable genetic display package that displays the polypeptide at the surface of the package and expressing in a recombinant organism a second polypeptide chain of said multimer and allowing the polypeptide chains to come together to form a multimer(see column 2, lines 51-59). Dower et al teach that the preferred vectors are filamentous phage fd, f1, and M13 (see column 2, lines 47-48). The reference teaches expression of nucleic acid of each polypeptide chain that is capable of being packaged as replicable genetic display package (see columns 1-2). The reference teaches a method to obtain nucleic acid encoding at least one of said first and second polypeptide chains

from a library of nucleic acids encoding said chain (see column 12, lines 49-50). Dower et al teach fusion with pIII coat protein (capsid protein) thus the fusion with the capsid protein is displayed on the phage coat protein while the non-fused protein is expressed in wild type form. The reference teaches that a DNA library is constructed by cloning cDNA (vH region) from the donor cells into a coat protein gene (gene III) cloning site, and the cloning sequences (vH domains) are ultimately expressed as polypeptides up to 120 amino acids (refers to the specific binding pair member is at least 100 amino acids of the instant claims). The reference teaches although a large peptide fragment near the N-terminus of the coat protein may cause a decrease in phage infectivity and/or yield compared to phage with smaller, but the larger fragments may still be effectively enriched by subsequent rounds of panning (see column 8). The reference teaches that the host cells are then infected with the phage and cultivated under conditions allowing for expression and assembly of phage particles, and the appropriate host cells for bacteriophage are various strains of E.coli (see column 6, lines 23-25). The reference method teaches to isolate phage which contain cloned library sequences which encode a desired protein and thus to ultimately isolate the nucleic acid sequences, phage harvested from the bacteria are affinity purified (see column 6, lines 54-58). Dower et al teach that the phage identified having an antibody recognized by the target are selected and DNA prepared and sequenced by standard methods to determine DNA and amino acid sequence of the particular antibody, and the DNA may be recloned in a suitable eukaryotic or prokaryotic expression vector and transfected into an appropriate host for production of large amounts of protein (see column 12).

Dower et al teach that the disclosed method of screening a DNA library for nucleotide sequence which encodes a protein of interest is typically an antibody or fragment thereof, but may also be any protein which may be cloned from a nucleotide library, and such proteins include, for example, hormones, interferons, interleukins and enzymes (see column 3, lines 18-24, in particular). Dower et al teach antibodies with catalytic activities (refers to enzymatic activity of the instant claims) may be enriched in groups of antibodies with high affinity for reactants but low affinity for products. A double screen to enrich for antibodies with these characteristics is useful in finding antibodies to catalyze reactions, and catalytic antibodies (refer to enzyme of the instant claims) capable of certain cleavage reactions may be selected using the disclosed method. For example a catalytic antibodies (refer to enzymes of the instant claims) capable of cleavage a specific amino acid from the end of a peptide (refers to desired ligand of instant claims) may be selected by immobilizing the peptide and panning the antibody library under conditions to promote binding but not cleavage and followed by wash, this allows antibodies that recognized the end group to bind and become immobilized, and to separate the antibodies capable of cleavage, the conditions are shifted in favor of cleavage, which would release the antibody-phage capable of cleavage from the immobilized peptide (see column 11, lines 29-51, in particular).

Dower et al teach that the method can be applied in therapeutic, diagnostic applications, and in preparation of catalytic antibodies. Dower et al teach that the disclosed method facilitate the screening process, thereby enabling DNA sequences which encode protein of interest, and particularly antibody molecules to be recloned and expressed, and these procedures may be used

to obtain an antibody to a preselected target molecule, thus, the difficulties and labor intensive process of generating monoclonal antibodies may be avoided.

The claimed invention differs from the prior art teachings by reciting that the specific binding pair is enzyme or fragment thereof is at least 200 amino acids. Dower et al do not specifically teach that the specific binding pair is 200 amino acids. However, Dower et al teach when the desired protein is a multichain protein, such as an antibody or binding fragment thereof (Fab), the chains (vH or vL) are cloned as separate libraries in a different plasmid vectors, amplified, and subsequently the fragments (vL fragments) are installed into the first chain-coat protein library vector (first chain-coat protein is an vH or fragment thereof which encodes a polypeptide of 120 amino acids), thus randomly combining vH and vL sequences in a single phage genome (vH and vL together would become more than 200 amino acids), and the number of possible combinations of heavy and light chains probably exceed 10^{12} (see column 9). Thus, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the method of screening a DNA library for nucleotide sequence which encodes a protein of interest taught by Dower et al to identify an enzyme or fragment which is 200 amino acids, because Dower et al teach catalytic antibodies (refers to enzymes of the instant claims) which are capable of cleavage(refers to desired enzymatic activity of the instant claims) and the reference teaches that vH domains (of antibodies) are expressed as polypeptides of about 120 amino acids, and when the desired protein is a multichain protein the reference teaches randomly combining libraries of vH and vL sequences in a single phage genome (vH and vL together are

more than 200 amino acids), and Dower et al teach the larger fragments may still be effectively enriched by subsequent rounds of panning (see column 8) using the disclosed method. A person of ordinary skill in the art would have been motivated to use the method taught by Dower et al to obtain a specific binding pair member comprises an enzyme of 100-200 amino acids, because Dower et al teach that the disclosed method is useful to screen for enzymes and the method can be applied in therapeutic, diagnostic applications.

17. Applicant's arguments filed on 10/10/00 regarding the art rejections of record have been fully considered but they are not persuasive.

Applicants argue that Dower does not provide any disclosure of an enzyme or fragment. Applicants arguments have been considered but are not persuasive, because Dower et al teach that the disclosed method of screening a DNA library for nucleotide sequence which encodes a protein of interest is typically an antibody or fragment thereof, but may also be any protein which may be cloned from a nucleotide library, and such proteins include, for example, hormones, interferons, interleukins and enzymes (see column 3, lines 18-24, in particular). Dower et al teach antibodies with catalytic activities which would read on the enzymes of the instant invention.

Applicants argue that 'enzyme' as used in the instant specification does not include antibodies. Applicants arguments have been considered but are not persuasive because the instant specification does not specifically disclose that the antibodies are not enzymes or enzymes do not include antibodies. The specification does not specifically teach any specific characteristics which

would not include antibodies as enzymes. Antibodies with catalytic activities could be used as enzymes.

Applicants argue that Dower does not provide 'library of nucleic acid sequences encoding a genetically diverse population of polypeptides are provided by mutation'. Applicants argue that Dower constructed the library from nucleic acids obtained from mammalian cells. Applicants arguments have been fully considered but are not persuasive, because Dower et al teach that the cDNA sequences representing the antigen binding domains of the heavy chain and light chains are synthesized form the RNA of the antibody producing cells or from the spleen cells; the cDNA is amplified using primers, and the amplified double stranded DNA are digested with restriction nuclease and ligated. Dower et al also teach that DNA from the light chain is digested and the large fragment is ligated with DNA of heavy chain library. Thus, Dower et al teach that the nucleic acid sequence would undergo mutation or recombination before it has been inserted into the vectors.

Applicants argue that Dower et al provide no motivation or suggestion of enzymes of 100 or 200 amino acids can be produced using phage display method. Dower et al disclosure of antibodies does not teach instantly claimed invention which is directed to enzymes. Applicants arguments have been considered but are not persuasive. Dower et al specifically do not teach phage display library of enzymes, but teach phage display library of catalytic antibodies, which would read on the enzymes of the instant claims. Applicants argue that prior to the instant invention, it was not known in the art to display at the surface of phage particle, a polypeptide

that is larger than about 100 amino acids. Applicants also pointed out the prior art references published in 1988, that the phage would not display larger proteins, and the larger inserts would disrupt the function of the gene III. Applicants argue that the present invention, for the first time provided a disclosure of bacteriophage display of function al protein domains having at least 100 amino acids. Applicants arguments have been considered but are not persuasive. Dower et al teach that a DNA library is constructed by cloning cDNA (vH region) from the donor cells into a coat protein gene (gene III) cloning site, and the cloning sequences (vH domains) are ultimately expressed as polypeptides up to 120 amino acids (refers to the specific binding pair member is at least 100 amino acids of the instant claims). Thus, for the reasons of record the rejections of record have been maintained.

18. No claims are allowed.

19. Art references C156-C170 listed by applicant on Form 1449 filed on November 24, 2000 were not considered by the examiner because they fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 (Author, Title, date and pertinent pages of the documents are not provided). These documents have been placed in the application file, but the information referred to therein has not been considered as to the merits.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner can normally be reached on Monday to Thursday from 6.30 AM to 4.00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached at (703)308-2439. The fax number for this group is (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

P. Ponnaluri
Patent Examiner
Technology center 1600
Art Unit 1627
10 January 2001